Pancreatitis and Diabetic Ketoacidosis with Quetiapine Use

by JAVAID RASHID, MD; PERRY J. STARER, MD; and SHAZIA JAVAID, MD

Dr. Rashid is Assistant Professor of Psychiatry, SUNY Downstate and Attending Psychiatrist, Kings-boro Psychiatric Center, Brooklyn, New York; Dr. Starer is Assistant Professor, Department of Geriatrics and Adult Development, Mount Sinai School of Medicine and Associate Attending Physician, Mount Sinai Services, Elmhurst Hospital Center, New York, New York; and Dr. Javaid is Research Associate, International Medical Graduate, Brooklyn, New York.

Psychiatry (Edgemont) 2009;6(5):34–37

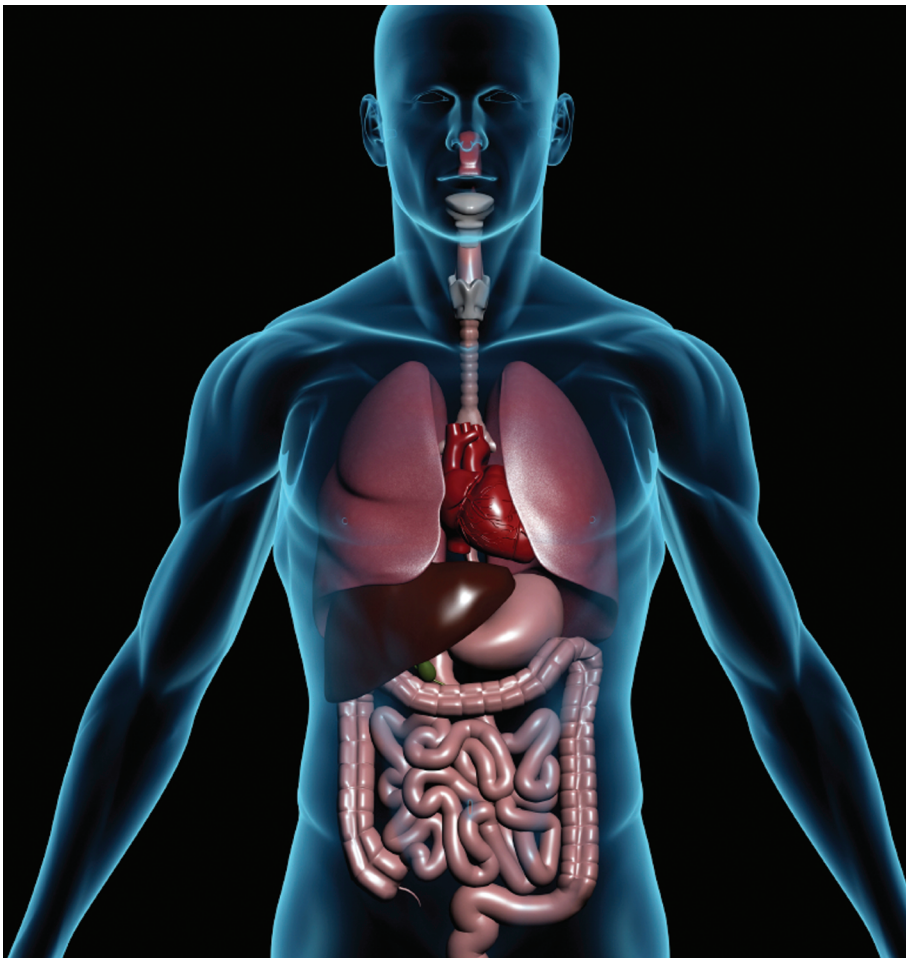
ABSTRACT

There have been case reports about second-generation antipsychotics causing pancreatitis. In addition, there has been a case report of pancreatitis without diabetic ketoacidosis associated with the use of quetiapine, specifically, and a case report of a patient receiving quetiapine who rapidly developed hyperglycemia and acidosis without evidence of acute or chronic pancreatitis. We present what we believe to be the first report of a patient who developed pancreatitis and life-threatening diabetic ketoacidosis while receiving quetiapine.

CASE REPORT

A 30-year-old Bengali woman with a history of schizophrenia with prominent negative symptoms presented to the emergency room with the complaint of diffuse abdominal pain present for two days. She also complained of polyuria and polydipsia and reported vomiting twice in the preceding day. She reported no history of fever, chills, chest pain, or cough. There had been no recent change in her weight.

She had a history of polycystic ovary disease. There was no history of diabetes mellitus. There was no known history of hypertriglyceridemia. There was no history of alcohol abuse. There was no family history of diabetes mellitus. Nine months before presentation, she was treated for schizophrenia with ziprasidone



FUNDING: There was no funding for this article.

FINANCIAL DISCLOSURE: The authors report no relevant conflicts of interest or commercial ties with respect to this material.

ADDRESS CORRESPONDENCE TO: Javaid Rashid, MD, 75 Ave U, # 1R, Brooklyn, NY 11223; Phone: (718) 946-9329; Fax: (718) 946-9329; E-mail: kbmdjrr@omh.state.ny.us

KEY WORDS: quetiapine, antipsychotics, pancreatitis, DKA, diabetic ketoacidosis

(Geodon®), starting at 20mg orally, twice daily, and slowly titrated up to 80mg orally, twice daily, over a three-week period. She continued to exhibit psychotic symptoms, so quetiapine (Seroquel®) was added to augment the response, starting at 25mg orally, at bedtime, two months after the ziprasidone initiation. The dose of quetiapine was slowly titrated up to 200mg orally, at bedtime. At current presentation, she was taking ziprasidone 80mg orally, twice daily, and quetiapine 200mg orally, at bedtime. She was not taking any other psychiatric medications and was clinically stable.

Initial physical examination revealed a woman with mild obesity and hirsuitism. Her temperature was 97.6 degrees Fahrenheit, blood pressure was 136/91mmHg, pulse was 91 beats per minute, and respiratory rate was 18 breaths per minute. Her abdomen was soft with positive bowel sounds without any tenderness or guarding. She had no other positive signs on physical examination. She had a blood glucose of 1081mg/dL with 4+ acetone. Her white blood cell count was 20.6K/mm^3, hemoglobin was 16.7g/dL, hematocrit was 50.4 percent, and platelet count was 439K/mm^3. Her triglyceride level was 537mg/dL on admission. Her alkaline phoshatase was 119U/L, alanine aminotransferase was 28U/L, aspartate transaminase was 25U/L, and bilirubin was 1.3mg/dL.

The patient was admitted to the intensive care unit and was treated for diabetic ketoacidosis. Further blood tests showed amylase of 550IU/L and lipase 982IU/L. Computed tomography (CT) scan of the abdomen showed moderate acute pancreatitis with no peripancreatic fluid or abscess with moderate left-sided pleural effusion and a small right-sided pleural effusion. Abdominal ultrasonography showed gallbladder sludge. The patient was treated with intravenous fluids and analgesic medications.

The psychiatry consultant discontinued quetiapine and ziprasidone and initiated treatment with haloperidol. The patient became medically stable after three days of hospitalization. Her amylase level decreased to 114IU/L and lipase level decreased to 126IU/L The patient was discharged to her home with appointments for follow up by the endocrinology and psychiatry services.

DISCUSSION

Causes of acute pancreatitis include gallstones, alcohol use, hypertriglyceridemia, medication toxicity, trauma from endoscopic retrograde cholangiopancreatography, hypercalcemia, abdominal trauma, various infections, autoimmune, ischemia, and hereditary causes.[1] A history of alcohol use was not present in this case. Possible etiologies of acute pancreatitis in this case include hypertriglyceridemia, biliary sludge, and medication. Biliary sludge, which may also be known as microlithiasis, was seen on this patient's abdominal sonogram. The causal relationship between microlithiasis and pancreatitis is uncertain.[2,3] In a study of patients with gallbladder sludge without stones or other gallbladder abnormalities, acute pancreatitis was not observed for at least for the first year after sludge development.[4] When assessed early after the onset of abdominal pain, serum increases of aminotransferases, especially alanine aminotransferase (ALT), are suggestive of microlithiasis in idiopathic acute pancreatitis.[5]

Extreme elevations of triglyceride levels (more than 1,000mg/dL) have been causally linked to acute pancreatitis.[6,7] Mild to moderate hyperlipidemia can be observed secondary to acute pancreatitis and should not be confused with the marked hypertriglyceridemia that causes acute pancreatitis.[7]

The use of second-generation antipsychotic medications, including olanzapine and clozapine, has been associated with pancreatitis.[8–13] Gropper and Jackson reported three cases in which patients developed either acute or chronic pancreatitis while receiving quetiapine.[14] In two of these cases, valproic acid, which is known to induce pancreatitis,[15] was also being administered.[14] A third patient was taking quetiapine without receiving valproate.[14] In all three cases, symptoms of pancreatitis appeared shortly after the initiation of quetiapine.[14,15]

There are little mechanistic data available concerning the link between second-generation antipsychotic medications and acute pancreatitis.[16]

Second-generation antipsychotic medication use may unmask or precipitate hyperglycemia[17,18] and has been associated with the development of both obesity and new-onset diabetes.[19] New-onset diabetes mellitus may develop within one year of initiation of second-generation antipsychotic treatment, but is not necessarily associated with weight gain.[20]

Quetiapine therapy is associated with moderate weight gain during both short- and long-term treatment.[21] Quetiapine treatment has been reported to be associated with the development of hyperglycemia[17] and new-onset diabetes mellitus,[22] with most cases of hyperglycemia occurring within three months.[17] However, quetiapine therapy is not associated with a consistent increase in the risk of developing diabetes.[21] The risk is not eliminated with extended therapy, and the onset of hyperglycemia may be rapid and severe.[17] In addition, there has been a report of a patient who developed both diabetes mellitus and hypertriglyceridemia in association with the use of quetiapine.[23]

In patients with no previous history of diabetes mellitus, second-generation antipsychotic medications, such as olanzapine, have been associated with hyperglycemia and acidosis.[24,25] The first presentation of diabetes mellitus associated with a second-generation antipsychotic medication may be diabetic ketoacidosis requiring admission to an intensive care unit.[20]

There has been a case report of an elderly patient receiving a low dose of quetiapine who rapidly developed hyperglycemia and acidosis without evidence of acute or chronic pancreatitis.[26]

Severe hypertriglyceridemia (>600mg/dL) has been associated with olanzapine and quetiapine therapy.[21] Some of these patients also developed new-onset diabetes.[19] Although large triglyceride increases are seen

occasionally in patients receiving second-generation antipsychotic medications, the causes for the severe hypertriglyceridemia are unclear.[19] 5-HT 2c receptor-deficient mice have been reported to be overweight as a result of abnormal control of feeding behavior.[27] Consideration has been given to the antagonistic effect of clozapine, olanzapine, and quetiapine on the 5-HT 2c receptor, which has been implicated in hyperphagia and the subsequent development of obesity and adult-onset diabetes, but has not been implicated in the direct inducement of hyperlipidemia.[19]

Moderate hypertriglyceridemia is common during episodes of diabetic ketoacidosis.[28] In patients with diabetic ketoacidosis, increases in serum levels of pancreatic enzymes may not indicate the presence of acute pancreatitis because elevations have been found to correlate with hyperglycemia, dehydration, and acidosis.[29,30] In the case presented here, there was also radiologic evidence of pancreatitis.

Severe hypertriglyceridemia has been proposed as a mechanism by which diabetic ketoacidosis could lead to acute pancreatitis.[31] However, severe hypertriglyceridemia was not observed in our patient.

When reviewing this case, it is important to consider this patient's risk factors for hyperglycemia and pancreatitis. Although new-onset diabetes mellitus may not be associated with weight gain during treatment with second-generation antipsychotic agents, patients who are overweight before initiation of second-generation antipsychotic agents may be at risk for diabetes mellitus or diabetic ketoacidosis.[20]

This patient's risk factors for developing glucose intolerance and type 2 diabetes mellitus included polycystic ovary disease[32] and being overweight. It is possible that these factors, rather than the quetiapine, were the cause of pancreatitis and diabetic ketoacidosis. However, the patient did not develop pancreatitis and diabetic ketoacidosis until initiation of quetiapine, despite the preexistence of these other risk factors. Due to the preexisting risk factors, it is likely the patient was more susceptible to the adverse effects of quetiapine.

This patient was also receiving ziprasidone, which is associated with a minimal effect on body weight and adiposity and is not associated with an increase in the risk of developing diabetes or dyslipidemia.[21] There has been a report of pancreatitis and hyperglycemia associated with the use of ziprasidone.[33] However, this occurred in the setting of rhabdomyolysis, hypertension, and fever, which is suggestieve of the presence of neuroleptic malignant syndrome.

We conclude that this was a case of pancreatitis related to the use of a low dose of quetiapine in association with ziprasidone. Other possible causes of pancreatitis were considered less likely. The pancreatitis led to life-threatening diabetic ketoacidosis.

CONCLUSION

Even when used at a low dose, quetiapine may be associated with the development of pancreatitis and diabetic ketoacidosis. Routine amylase level monitoring has been recommended for patients treated with high doses of clozapine.[34] Consideration should also be given to monitoring the amylase levels of patients receiving quetiapine, even if it is being administered at a low dose and especially if used in combination with another atypical antipsychotic medication.

Weight, plasma glucose, and lipid levels should be regularly monitored in patients receiving antipsychotic medications, according to published guidelines.[19,20,23,35,36]

The association of quetiapine use with hyperglycemia and diabetes mellitus is not clearly dose-dependent, and the most severe hyperglycemia has been observed in patients without previously diagnosed diabetes who were not monitoring glycemic control.[17] Since hyperglycemia associated with quetiapine can be unpredictable, physicians should monitor patients for weight gain, hyperglycemia, and dyslipidemia.[37] These patients also require monitoring for the clinical signs of diabetes mellitus, including excessive thirst, frequent urination, fatigue, and unexplained weight loss.[19] Weight gain alone is not a sufficient predictor of the development of hyperglycemia and acidosis.[38]

Screening for the development of diabetes mellitus in patients with polycystic ovarian syndrome has been recommended because of the high prevalence of glucose intolerance attributed to the insulin resistance, which is present in both women who are lean and women who are obese.[32] Patients who are predisposed to the development of diabetes mellitus who are also receiving quetiapine should be monitored for the development of diabetes mellitus.

According to the guidelines of the American Diabetes Association (ADA) and the American Psychiatric Association, patients receiving second-generation antipsychotic drugs should receive baseline screening and ongoing monitoring of plasma glucose and lipid levels.[36] Unfortunately, even though these guidelines recommending testing in patients receiving second-generation antipsychotics were issued in February 2004 by the ADA, plasma lipid and glucose testing rates have remained low.[37] It is essential for clinicians to recognize the importance of monitoring metabolic risk in patients receiving second-generation antipsychotic drugs.[39]

REFERENCES

1. Cappell MS. Acute pancreatitis: etiology, clinical presentation, diagnosis, and therapy. *Med Clin North Am.* 2008;4:889–923.
2. Lee SP, Nichols JF, Park HZ. Biliary sludge as a cause of acute pancreatitis. *N Engl J Med.* 1992;326:589.
3. Levy MJ. The hunt for microlithiiasis in idiopathic recurrent pancreatitis: Should we abandon the search or intensify our efforts? *Gastrointest Endosc.* 2002;2:55.
4. Janowitz P, Kratzer W, Zemmler T, et al. Gallbladder sludge: spontaneous course and incidence of complications in patients without stones. *Hepatology.* 1994;20:291–294.

5. Grau F, Almela P, Aparisi L, et al. Usefulness of alanine and aspartate aminotransferases in the diagnosis of microlithiasis in idiopathic acute pancreatitis. *Int J Pancreatol.* 1999;2:107–111.
6. Toskes PP. Hyperlipidemic pancreatitis. *Gastroenterol Clin North Am.* 1990;4:783–791.
7. Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. *J Clin Gastroenterol.* 2003;1:54-62.
8. Bergemann N, Ehrig C, Diebold K, et al. Asymptomatic pancreatitis associated with clozapine. *Pharmacopsychiatry.* 1999;32:78–80.
9. Doucette DE, Grenier JP, Robertson PS. Olanzapine-induced acute pancreatitis. *Ann Pharmacother.* 2000;34:1128–1131.
10. Frankenburg FR, Kando J. Eosinophilia, clozapine, and pancreatitis. *Lancet.* 1992;340:251.
11. Gatto EM, Castronuovo AP, Uribe Roca MC. Clozapine and pancreatitis. *Clin Neuropharmacol.* 1998;21:203.
12. Hagger R, Brown C, Hurley P. Olanzapine and pancreatitis. *Br J Psychiatry.* 2000;177:567.
13. Martin A. Acute pancreatitis associated with clozapine use. *Am J Psychiatry.* 1992;149:714.
14. Gropper D, Jackson CW. Pancreatitis associated with quetiapine use. *J Clin Psychopharmacol.* 2004; 3:343–345.
15. Chapman SA, Wacksman GP, Patterson BD. Pancreatitis associated with valproic acid: a review of the literature. *Pharmacotherapy.* 2001;12:1549–1560.
16. Kahn D, Bourgeois JA. *J Clin Psychopharmacol.* 2007;4:397–400.
17. Koller EA, Weber J, Doraiswamy PM, Schneider BS. A survey of reports of quetiapine-associated hyperglycemia and diabetes mellitus. *J Clin Psychiatry.* 2004;6:857-63.
18. Wilson DR, D'Souza L, Sarkar N, Newton M, Hammond C. New-onset diabetes and ketoacidosis with atypical antipsychotics. Schizophr Res. 2003;1:1-6.
19. Meyer JM. Novel antipsychotics and severe hyperlipidemia. *J Clin Psychopharmacol.* 2001;21:369–374.
20. Jin H, Meyer JM, Jeste DV. Phenomenology of and risk factors for new-onset diabetes mellitus and diabetic ketoacidosis associated with atypical antipsychotics: an analysis of 45 published cases. *Ann Clin Psychiatry.* 2002;1:59–64.
21. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs.* 2005;19(Suppl 1):1–93.
22. Sobel M, Jaggers ED, Franz MA. New-onset diabetes mellitus associated with the initiation of quetiapine treatment. *J Clin Psychiatry.* 1999;8:556–557.
23. Yamauchi T, Tice A. Metabolic abnormalities associated with atypical antipsychotics: a case report and alert. *Hawaii Med J.* 2007; 1:12–13.
24. Ragucci KR, Wells BJ. Olanzapine-induced diabetic ketoacidosis. Ann Pharmacother. 2001;12:1556–1568.
25. Varma MK, Connolly K, Fulton B. Life-threatening hyperglycemia and acidosis related to olanzapine: a case report and review of the literature. *J Intensive Care Med.* 2007;1:52–55.
26. Takahashi M, Ohishi S, Katsumi C, et al. Rapid onset of quetiapine-induced diabetic ketoacidosis in an elderly patient: a case report. *Pharmacopsychiatry.* 2005;4:183–184.
27. Tecott LH, Sun LM, Akana SF, et al. Eating disorder and epilepsy in mice lacking 5-HT2C serotonin receptors. *Nature.* 2002;374:542–546.
28. Fulop M, Eder HA. Plasma triglycerides and cholesterol in diabetic ketosis. *Arch Intern Med.* 1989;9:1997–2002.
29. Vantyghem MC, Haye S, Balduyck M, et al. Changes in serum amylase, lipase and leukocyte elastase during diabetic ketoacidosis and poorly controlled diabetes. *Acta Diabetol.* 1999;36(1-2):39–44.
30. Warshaw AL, Feller ER, Lee KH. On the cause of raised serum-amylase in diabetic ketoacidosis. *Lancet.* 1977;8018:929–931.
31. Nair S, Yadav D, Pitchumoni CS. Association of diabetic ketoacidosis and acute pancreatitis: observations in 100 consecutive episodes of DKA. *Am J Gastroenterol.* 2000;10:2795–2800.
32. Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nestler JE. Glucose intolerance in polycystic ovary syndrome—a position statement of the Androgen Excess Society. *J Clin Endocrinol Metab.* 2007;12:4546–4556.
33. Yang SH, McNeely MJ. Rhabdomyolysis, pancreatitis, and hyperglycemia with ziprasidone. Am J Psychiatry. 2002;8:1435.
34. Jubert P. Clozapine-related Pancreatitis. *Ann Intern Med.* 1994;9:722–723.
35. Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. *J Clin Psychiatry.* 2001;62[suppl 27]:15–26.
36. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care. 2004 Feb;27(2):596-601
37. Marlowe KF, Howard D, Chung A. New onset diabetes with ketoacidosis attributed to quetiapine. *South Med J.* 2007;8:829-31.
38. Haupt DW, Rosenblatt LC, kim E, Baker RA, Whitehead R, Newcomer JW. Prevalence and predictors of lipid and glucose monitoring in commercially insured patients treated with second generation antipsychotic agents. *Am J Psychiatry.* 2009; 166(3): 345-53
39. Morrato EH, Newcomer JW, Allen RR, Valuck RJ. Prevalence of baseline serum glucose and lipid testing in users of second-generation antipsychotic drugs: a retrospective, population-based study of Medicaid claims data. *J Clinical Psychiatry.* 2008; 69(2): 316-22.